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COUGH REMEDIES

Over 600 ethical and over-the-counter cough remedies are listed in drug trade manuals. Most are shotgun mixtures containing varying—and often inadequate—concentrations of "antitussives" (cough-center depressants), expectorant salts, antihistamines, bronchodilators, and other drugs traditionally employed in cough mixtures. Whatever the mechanism of the cough disturbance, some pellets from the shotgun, it is hoped, will reach the target.

Cough is considered a protective reflex which can often be disregarded, but when the cough interferes with sleep or with eating, or causes vomiting, pain, dyspnea or heart strain, treatment is called for. Cough is always a symptom, however, and rational treatment is possible only when the cause has been determined.

SOME SPECIFIC MEASURES - Treatment of cough should, if possible, start with measures aimed at the underlying disease. An appropriate antibacterial agent is the best cough remedy when the cough is due to a bacterial infection of the respiratory tract. Diuretics and digitalis are the most effective drugs for the relief of cough due to heart failure. The control of environmental factors which aggravate a cough, such as tobacco smoke or excessively dry indoor air, is often more effective than an antitussive drug. Where a benign cough provokes excessive anxiety or is a conversion symptom of hysteria, an appropriate sedative and psychologic support will be more effective than any cough remedy.

When specific therapy is not possible or is ineffective, cough-relieving measures may be necessary. Disorders of the upper-respiratory tract such as the common cold are usually self-limited; if anything more than reassurance is needed, steam inhalation may be helpful, and non-medicated candy drops may be useful for their demulcent effect; there is no need for, and it is safer not to prescribe, medicated lozenges and troches.

In disorders arising below the epiglottis, cough remedies—oral, parenteral, inhalant or aerosol—are often required. For the cough associated with bronchospasm (as in asthma, chronic bronchitis and pulmonary emphysema) a bronchodilating drug such as ephedrine is the first choice. An expectorant drug such as potassium iodide may also be useful in liquefying thick secretions. Other traditional expectorants include the ammonium salts, antimony potassium tartrate,

terpin hydrate, guaiacol, creosote, squill, and ipecac. All of these drugs reflexly augment the output of respiratory-tract fluid. To be effective, they must be taken in doses approaching maximum tolerance. Steam inhalation and forcing of fluids are sometimes more effective in loosening tenacious sputum or in relieving a dry cough than the use of expectorant drugs.

OPIATES - Codeine is the classic antitussive drug, but investigators still disagree as to its clinical effects. Carefully controlled studies with pathological rather than experimental cough have shown that ordinary doses of codeine have relatively little effect on frequency of cough; nevertheless, patients feel that they are helped - an important consideration. Opiates in wide use for the treatment of cough also include dihydrocodeinone (Hycodan - Endo; Dicodid - Knoll; Tussionex - Strasenburgh, and other brands), methadone (various manufacturers), meperidine (Demerol - Winthrop), and levorphanol tartrate (Levo-Dromoran Tartrate - Roche). Some clinicians prefer morphine for short-term relief of severe cough (H. Gold, Cornell Conference on Therapy, 5:1, 1952). While these narcotic agents are potentially addicting, their use in an acute coughing disturbance is quite safe. In chronic bronchitis and other chronic disorders, narcotic cough mixtures are best avoided. There is no basis for the recommendation of any one narcotic over others. Dihydrocodeinone appears to have no advantage over codeine in equipotent doses.

NON-ADDICTING ANTITUSSIVES - A number of non-addicting compounds claimed to depress the cough center have been marketed in recent years. These include dextromethorphan hydrobromide (Romilar - Roche, and other brands), noscapine (Nectadon - Merck, and in various combinations), carbetapentane salts (Toclase - Pfizer; Rynatuss - Neisler), caramiphen ethanedisulfonate (Toryn Syrup - SKF), and dimethoxanate (Cothera Syrup - Ayerst). Clophedianol (Ulo Syrup - Riker) and benzonatate (Tessalon - Ciba) are new antitussive agents which have not had sufficient clinical trial to permit evaluation. Tessalon is claimed to act peripherally as well as centrally, by depression of the "stretch (Hering-Breuer) reflex" of the lungs. If clinical studies support the claim, the drug could represent a useful development in cough remedies.

Most of the evidence supporting the special claims for various antitussive drugs leaves a great deal to be desired. In controlled studies, the results are seldom impressive. Thus, in a study by L. Cass, et al. (Am. J. Med. Sci., 227:291, 1954) the effects of dextromethorphan and of codeine, while considered "statistically significant," were meager. On a scale ranging from "0" (no cough) to "4" (incessant and distressing cough) the active drug was only 0.2 points more effective than the placebo. The emphasis in claims for the newer drugs is often placed on lower incidence of side effects, but as experience constantly shows, the apparent absence of side effects with a new drug does not mean that side effects will not show up with wider use of the drug.

ANTIHISTAMINES - Antihistamines are used in many cough remedies. The amount present in each dose of a typical preparation varies from a twelfth to a half of the dose required for the relief of an allergic disorder. Antihistamines in full doses are sometimes effective in relieving cough associated with bronchospasm, but the drying effect of such doses can be undesirable in some respiratory

infections. The sedative action of many antihistamines may help relieve the anxiety accompanying a severe cough. If an antihistamine is thought useful, it should be prescribed separately and in full doses.

Dry air usually aggravates a cough; when a winter cough is severe enough to require treatment, vaporizers or other means should, if possible, be used to maintain relatively high humidity in the patient's room.

OXAINE

Oxaine (Wyeth), a combination of a bis-acetamide (0.2% oxethazaine hydrochloride) and an aluminum hydroxide gel, is offered for the treatment of chronic gastritis, chronic esophagitis, "irritable bowel syndrome," and other gastrointestinal disorders. Although oxethazaine has demonstrated local anesthetic effects in the rabbit's eye, there are no published reports showing that it has a local anesthetic effect on the gastric mucosa in the concentration employed in Oxaine.

PUBLISHED EVIDENCE - The only published clinical evidence of the effects of Oxaine in chronic gastritis is an uncontrolled study by E. Deutsch and H. J. Christian (JAMA, 169:2012, 1959). Eighty per cent of the 92 patients in the study had "chronic gastritis" caused by or associated with other organic disease such as peptic ulcer. The combination was administered for periods ranging from six days to 18 months, along with such measures as bed rest, sedatives, gastric suction and special diets. The authors report that Oxaine gave "complete relief" of pain and distress for two to six hours after each dose in 94 per cent of the patients.

The use of Oxaine for symptomatic relief of chronic esophagitis finds support in a study by I. R. Jankelson and O. M. Jankelson (Am. J. Gastroent., 32:636, 1959), but this study also lacked adequate controls. And the only published evidence for the use of Oxaine in relief of "irritable bowel syndrome" is an uncontrolled study of six cases reported by the same authors (Am. J. Gastroent., 32: 719, 1959).

PLACEBO EFFECTS - The hazard of relying on uncontrolled trials, especially in conditions markedly affected by emotional factors, has been frequently emphasized in The Medical Letter. Just how unreliable uncontrolled studies may be in a study of gastrointestinal complaints can be judged from a report on "Placebo Effect in Peptic Ulcer and Other Gastroduodenal Disorders," by H. Backman, et al. (Gastroenterologia, 94:11, 1960). In summarizing their study, the authors write, "The effect on pain and other subjective complaints of tablet medication per se in peptic ulcer, gastritis, gastroduodenitis, gastric hypersecretion and gastric dyspepsia was studied by the double-blind placebo technique with the patients as their own controls. Placebo effect of tablet medication per se, i.e. the administration of tablets itself, brought about an improvement in the subjective symptoms of 157 out of 170 patients, i.e. 92 per cent."

TOXIC AND SIDE EFFECTS - No significant toxic or side effects were reported in the clinical studies of Oxaine. Too little is known of the pharmacol-

ogy and toxicology of oxethazaine hydrochloride, however, to permit casual use. Caution is also necessary in ascribing upper gastrointestinal pain and other dyspeptic symptoms to "chronic gastritis" or "chronic esophagitis." The symptoms may be due to much more common disorders such as peptic ulcer, hiatus hernia, gall bladder disease, pancreatitis, and other disorders both in and out of the gastrointestinal tract.

Medical Letter editors consulted many gastroenterologists, pharmacologists, and authorities on anesthetic agents in appraising Oxaine. None felt that the few clinical trials cited by the manufacturer provided adequate evidence for the effectiveness of the drug. The consultants differed, however, as to whether such a drug could be significantly more effective than a placebo and whether it might under any circumstances be worth a trial. If Oxaine is employed for symptomatic relief of gastrointestinal disorders, it should not obscure the need for accurate diagnosis and more specific therapy.

CHLORAL HYDRATE

Noctec (Squibb), Somnos (Merck) and Felsules (Fellows) are among a number of chloral hydrate preparations promoted as potent hypnotics virtually free of side effects. Chloral hydrate is prescribed much less frequently today than in the past, partly because of the effective promotion of newer hypnotics and "tranquilizers." It is, however, one of the best somnifacient drugs (L. Lasagna, J. Pharm. & Exper. Ther., 111: 9, 1954). Although standard drug reference books attribute frequent gastric side effects to chloral hydrate, it is quite free of such effects when taken as an elixir, in capsules, or dissolved in milk. Mental excitement is probably a much less frequent side effect with chloral hydrate than with other hypnotics. The incidence of hangover and of tolerance to the drug is also low.

DOSAGE - The effective adult dose of chloral hydrate varies from 1 to 2 grams; sleep is generally produced within an hour and lasts for five hours or more. Although detoxification of chloral hydrate and its active metabolite, trichloroethanol, occurs in the liver, and the products of its metabolism are excreted by the kidney, the drug can be safely used (in somewhat reduced dosage) by patients with liver or kidney disease. The traditional text-book contraindication to its use in cardiac patients is not justified by actual clinical experience.

FORMS AND COSTS - Because of its bitter taste, chloral hydrate is often taken in capsule form. It is also available in elixir and syrup forms, and it can be made up by the druggist as a flavored or unflavored solution (one grain per drop) to be mixed with milk or other food. It is also available in suppository form (Rectules - Fellows). In quantities of 100, half-gram (7.5-grain) capsules cost about 8¢ apiece, or about 15¢ for a one-gram dose. The prepared liquid preparations cost about the same for equal dosage. A one-grain-per-drop solution made up by the druggist costs only about 3 or 4¢ per gram. A 1.3-gram suppository costs about 40¢.

Chloral hydrate is a valuable hypnotic which could well be the drug of first choice for many patients.

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